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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/585,475	06/02/2000	N. Leigh Anderson	40488	6582

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EXAMINER

WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
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1652

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DATE MAILED: 05/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/585,475	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-94,96 and 97 is/are pending in the application.
- 4a) Of the above claim(s) 14-84 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 85-94,96 and 97 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ | 6) <input type="checkbox"/> Other: _____ |

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The Amendment under 37 CFR § 1.111 filed on February 12, 2003 as paper No. 14 is acknowledged. The amendments the claims have been entered as requested. Claims 1-6, 10-13 and 95 are cancelled; claims 85, 86, 89, 91, 93, 94 are amended. New claims 96 and 97 are added. Claims 14-94 and 96 to 97 are pending in the application, claims 85-94 and 96-97 are the subject of this Office Action; claims 14-84 are withdrawn from consideration as drawn to the non-elected invention.

Office Action

1. Objections

Claim 85 is objected to for numerous typographical errors. All the names of proteins should start with small letter. Line 12 contains unnecessary "N-G"; line 14 unnecessary "liver"; the abbreviation "eff. of apopt." in line 23 should be expanded.

2. Rejections

2.1 35 USC, section 112, second paragraph

Rejection of claims 1-6, 10-13 and 95 under this paragraph, made in the previous Office Action, paper No. 10 is moot, because the claims have been cancelled. However claim 85-94 and 96-07 are still rejected for the use of term "a degree of efficacy" of an agent, because neither the claims nor the specification define the term efficacy. It is unknown to what the word efficacy is related. Is this an efficacy of a drug in the treatment of a

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particular disorder? How the degree of efficacy is defined? The indefinite term and phrase render the claims indefinite.

In their response Applicants write that the term efficacy means, according to dictionary, "the power to produce an effect", and, as an example, Applicants quote the following passage from the specification "The degree of its [cytosolic HMG-CoA synthase] induction thus may reflect the pharmacological potency of an HMG-CoA reductase inhibitor to inhibit HMG-CoA reductase and hence serves as a marker to compare efficacy among members of the statin family of compounds and between families of chemically unrelated agents with a similar mode of action." (Emphasis added by Applicants).

This argument has been fully considered but is found not persuasive for the following reasons. The above dictionary definition is acknowledged. However, the meaning of the term is unclear absent a statement of what effect is referred to. While some "effects" might be obvious on their face from an agent, many compound included within the scope of "agent" would not have any associated effect or may have multiple different effects. The general, not questionable meaning of the term has too broad scope, and one skilled in the art would not know what is included or excluded from the scope of the claim. The meaning of the term efficacy as described in the quoted passage is a definite meaning, however, this meaning is not use by the claims. Thus, as stated in the previous Office Action, paper No. 10, in order to examine claim 85, it is assumed that

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the efficacy of an agent is any change it causes in the kind and content (concentration in the tissue) of the proteins isolated from the exposed tissue as compared to unexposed tissue or the same tissue exposed to an agent for which said changes are already known. In addition, claim 88 recites the phrase "relative amount of toxicity or effectiveness", which is not defined in the claim or the specification.

Claims 96 recites the terms "effective amount" and "greater than effective amount", which are not defined by the claim or specification. The claims and specification do not define what the amount must be effective for.

Claim 86, being dependent on claim 85 is directed to the MSNs that are not recited by the base claim. MSN 34, 42, 59, 66 and 69 are not included in the scope of claim 85. Thus, claim 86 broadens the scope of the base claim, thus claim 86 is improperly dependent.

2.2. 35 USC section 112, first paragraph

Rejection of claim 85-94 and new claims 96-97 are rejected under 35 U.S.C. 112, first paragraph for reasons made the previous Office Action, paper No.10 and reiterated herein.

The specification fails to describe a degree of toxicity and/or efficacy and its measurements. The disclosure is enabling for determining changes in the presence

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and/or level of markers in a proteome, wherein the changes are caused by exposure of a tissue to tested chemicals. On page 6, line 26 the Applicants write: "Sets of perturbed protein markers provide a proteomic pattern or 'signature' **INDICATING** [emphasis MW] relative toxicity and/or efficacy." Indicating does not mean quantifying a degree. The quoted passage means qualitative assay.

Examples presented by Applicant are silent about how to perform measurements of toxicity and efficacy. Thus, the disclosure is not enabling for a quantitative assay of toxicity/efficacy. The disclosure is enabling visualizing the changes in the proteome induced by any agent.

Applicants do not teach any calibration curve that would represent a relationship between toxic effects measured by, for example, increased blood transaminases (see page 15, line 9) and changes in the level of particular marker/markers in the proteome. The disclosure also fails to teach any calibration curve for efficacy of a drug, as for example a relationship between the level of cholesterol in the blood after treatment with a particular drug and a level of particular marker/markers in the proteome. In addition, the claimed subject matter is broad and includes unpredictable changes in the levels of proteins in the cell in response to the exposure to a drug or toxic agent. The quantity of some proteins may change in linear fashion; the amount of some proteins may be unaffected; some may disappear completely; some may change only after exposure to a certain threshold level of agent or may change in non-linear fashion. As such it would

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require undue experimentation to use any one or more protein markers to determine the efficiency or toxicity of a candidate agent absent guidance regarding how each marker changes in response to such agents and how the change correlate to toxicity and /or efficacy.

A skilled artisan concludes, therefore, the claimed subject matter was not described in the specification in such full, clear, concise and exact terms as to enable any person skilled in the art, to which it pertains, to use the invention.

In their response, Applicant refer the examiner to page 15, lines 18-26, the application teaches means to measure or to quantify proteins (page 9, line 5). This is however not responsive to the question how to measure the toxicity/efficacy.

Furthermore, Applicants write, "Regarding the suggested lack of guidance, certainly the specification provides a process whereby using different concentrations of a drug in contact with the system, patterns of proteins emerge where the patterns associated with efficacy and toxicity of said drug are identified."

The examiner has noted that the specification uses high and low dose of the tested drugs. The claims however, do not recite the measurement of toxicity and efficacy as determined at low and high doses of a drug. The claims are directed to the method that comprises "exposing a tissue of interest in a subject ". One skilled in the art understands

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the meaning of the phrase "exposing a tissue of interest in a subject " as the exposure to a single dose. In addition, claims 90, 93, 96 and 97 recite "pharmaceutically appropriate amount", "effective amount" and "toxic amount", respectively. Thus, there is no doubt that the claims are directed to single dose of an agent.

In conclusion, the current language of the claims refers to comparison of proteome of the tissue exposed to a dose of the tested drug with that of a dose of drug for which the characteristics of proteome is already known, or with proteome for unexposed control.

2.3. 35 USC section 103

Claims 85-92, inadvertently omitted claims 93-94 and new claims 96-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (A two-dimensional gel database of rat liver proteins useful in gene regulation and drug effects studies, *Electrophoresis*, **1991**, 12, 907-903) and Anderson et al. (An updated two-dimensional gel database of rat liver proteins useful in gene regulation and drug effect studies *Electrophoresis*, **1995**, 16, 1977-1981) and further in view of Anderson et al. (The effects of peroxisome proliferators on protein abundance in mouse liver, *Toxicology and Applied Pharmacology*, **1996**, 137, 75-89).

The claimed invention comprises testing an agent using display of proteome by two dimensional electrophoresis and measurements of levels of 175 protein markers listed in claim 85 and 112 markers listed in claim 86, wherein alternatively two control

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samples might be used. One of the controls is from the same tissue not treated with any agent, the other from the same tissue exposed to an agent of known toxicity or efficacy. Anderson and her co-workers exposed liver tissue in rats to antilipemic agents lovostatin, or lovostatin in combination with cholestyramine, or to none of the chemicals. The animals were sacrificed and livers removed, proteins extracted, and the levels of protein markers were measured in the liver proteome using two-dimensional electrophoresis. All protein markers listed in claim 85 and 86 of the instant application, total of 234, and at least three markers identified by full names in claim 85 of the instant application (actin gamma, apo A-I lipoprotein, HMG-CoA, and catalase) are already listed in Table 1 and 2 of Anderson 91 paper; see copies of the tables with marked positions. In addition, in her paper from 1995 Anderson provides further identification of the marker known previously as MSN. The markers listed in Anderson 95, in Table 1 on page 1978, are called "useful in drug effect studies". Table I of Anderson 1995 contains many markers listed in full names in claim 85 of the instant application; see the copy of Table 1 of Anderson 95 with examiners' markings of the respective markers.

Anderson et al. 1991, do not teach using alternatively two control samples; they use as control only unexposed sample. However, Anderson et al 1996 teach effects of peroxisome proliferators on mouse liver proteome. Among others, they study the drug called LY171883, at a range of doses, and they use an other peroxisome proliferator LY163443 as a negative control. The quantitative changes in amount of cytosolic

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epoxide hydrolase, 80 kDa bifunctional enzyme, and unidentified spot IEF163 induced by different doses of LY171883 are presented in Fig. 8, page 86; copy enclosed.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the method described by Anderson 1991, and if necessary, apply as a control the proteome from unexposed tissue, but also, as Anderson 1996 did, from the same tissue treated with an agent considered to be a standard in particular screening. In the art, it is routine to compare effects of two drugs, and it has been done with all methods known before the Applicants filed the application. Therefore, including, in alternative, the second control is not novel or inventive.

It would also have been obvious to one having ordinary skill in the art at the time of invention to have the method described in Anderson et al 1991, and modify it by using as markers of efficacy the markers of claims 85 and 86 of the instant Application because the very markers are listed by Anderson et al. as "protein useful in drug effect studies"; see the enclosed, marked, copy of Table 1 of Anderson et al. 1995.

The motivation would be to apply the proteome visualization in a method of screening for toxic and pharmacologic effects of potentially new drugs. This motivation is provided by Anderson et al. 1991, because their data, see Figure 10 and its description, clearly suggest that the proteome markers can be used to "show quantitative effects of various

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treatments" on mammalian tissue. The motivation is also provided by Anderson et al. 1996 by the title of the article.

The expectation of success is very high, because exposure of a tissue to a chemical always result in some changes in protein expression, synthesis and metabolism, and these changes are manifested by changes in the presence and/or level, of toxicity and/or efficacy markers in the proteome. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

In response to the rejection, Applicants write on page 17 line 15, "There is no specific suggestion for any of the specific claimed markers in Anderson et al. [Anderson et al. 1991, MW]. Moreover, Anderson et al. do not indicate the specific markers may be measured quantitatively in a manner that permits one to determine whether a candidate compound is more or less effective and/or more or less toxic than a known pharmaceutical or toxic compound."

Applicants' argument have been fully considered but is found not persuasive.

(1) Anderson's 1991 data certainly suggest that, for example HMG-CoA synthase is a good marker for measurements of efficacy of the antilipemic agents lovostatin and cholestyramine; see Fig.10 and 11 on page 921. In addition, to Anderson's

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1991, publications Anderson 1995 and 1995 clearly suggests all the markers listed in claim 85 and 86 as proper for studying effects of drugs.

(2) Andersons' et al data certainly indicate that the change in the level of specific marker, such as HMG-CoA synthase, MSN413, can be assessed as statistically significant at $p < 0.01$ or $p < 0.001$ over untreated control or between cholesteryl, cholestyramine and lovostatin; see Fig. 10 and 11 on page 921. When a suitable marker is identified for measurement after a specific treatment it is identified because the change of its concentration in the gel is measurable at the statistically significant level. In addition, Anderson et al 1996 clearly indicate that the specific markers, cytosolic epoxide hydrolase, 80 kDa bifunctional enzyme, and unidentified spot IEF163, all claimed in claim 1, may be measured quantitatively in a manner that permits one to determine whether a candidate compound is more or less effective than a known pharmaceutical or toxic compound.

Furthermore, on page 13, line 18, Applicants write Anderson et al 1991 do not show any dose response of effectiveness or toxicity et al.

This argument of applicant is found not persuasive in the light of the current version of 103 rejection. Anderson et al. 1996 do show dose response of induction of cytosolic epoxide hydrolase, 80 kDa bifunctional enzyme, and unidentified spot IEF163 when a mouse is treated with LY171883, see the enclosed copy of Fig. 8 of Anderson et al. 96.

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4. Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
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Patent Examiner

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